UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,108	04/06/2000	Kenneth Eliot Sherman		7634

7590 03/08/2007

CAROLINE NASH
NASH & TITUS, LLC
21402 UNISON ROAD
MIDDLEBURG, VA 20177

EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER
	20070305

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Please see the attached translation of a Chinese document by Huang et al. 1990, Virologica Sinica. This communication restarts the time period for response.

Agnieszka Boesen
3/5/2007

Stacey B. Chen
3/5/07

09/544 108

PTO 2007-2526

Article
Huang

Follow-up Observation on the Antiviral Effect of Combined Treatment of Small Dosage of Interferon and Thymosin in Patients with Chronic Hepatitis B

[小剂量干扰素与胸腺肽联合对慢性乙型肝炎抗病毒效应的追踪观察]

HUANG HUA-FANG

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. FEBRUARY 2007

Translated by: xxx

TITLE	Follow-up Observation on the Antiviral Effect of Combined Treatment of Small Dosage of Interferon and Thysomin in Patients with Chronic Hepatitis B
FOREIGN TITLE	小剂量干扰素与胸腺肽联合对慢性乙型肝炎抗病毒效应的追踪观察
Authors	Huang Hua-fang,Xiong Kie-jun,Wang Xin-He,Zeng Ling-lan,Liu Bi-xi
Author affiliation Source	Department of Infectious Disease, Union Hospital, Tongji Medical University, Wuhan, 430022)
Other Authors	Zeng Fan-zhen (Wuhan Bio-products Institute Wuhan) Wu Zhang-qi (Wuhan Institute of Virology, Academia Sinica, Wuhan)
Name of Journal	Virologica Sinica
Year	January, 1990
Pages	5

/1

In this paper, follow-up observations during one-half to 2 years were performed on 20 patients with chronic hepatitis B who had been treated by combining a small dosage of interferon with thymosin. Another 13 cases of chronic hepatitis B were treated with interferon alone with the same dosage and for the same period. The results showed that the negative percentage of HBeAge, HBcAg, DNAP, and HBV-DNA were 58.8%, 60%, 60% and 66.6%, respectively, in the treated group. In the contrast group, the negative percentage for the same indicators was 50%, 50%, 100%, and 50%, respectively. Then an observation was performed for HBV four replicated markers. Four cases were completely negative, 7 cases had only one positive marker, thus the total effect rate was 61.1% (11/18) in the treated group, while for the same indicator the rate in the contrast group was only 20% (2/10). The effect rate between the two groups was remarkably different ($p<0.01$). The antiviral effect of combined treatment was prominent in the contrast group. The varied methods used to strengthen the antiviral effect of interferon have been discussed. The results of the recent and follow-up period showed that the combined treatment of small dosage of interferon and thymosin was safe and effective. The combined treatment strengthens the antiviral effect, and should be further studied.

Key Words: Interferon Thymosin Antiviral treatment

We have reported[1] the observation on antiviral effect of combined treatment of small dosage of interferon and thymosin in

patients with chronic hepatitis B and concluded that the effect of combined treatment was better in recent periods of treatment. Now we give the follow-up observation of 20 patients who had been treated over half a year as follows:

Materials and Methods

1. Cases chosen:

All follow-up observations come from the patients with chronic hepatitis B who had been treated over half a year by a combined treatment of small doses of interferon and thymosin from September 1985 to April 1986. Up to October 1988, 1 case had been treated for half a year, 4 cases for 1 year, and 15 for 2 years. These cases included 12 males and 8 females. Their ages varied from 13 to 49, with an average age of 26.2.

Another 13 cases of chronic hepatitis B were treated with interferon alone, in the same dosage and for the same period as the contrast group to study the follow-up observation after over half a year's treatment, among which 2 cases had been treated for half a year, 2 for 1 year, and 9 for 2 years.

/2

2. Examination Items

Examine antigens and antibodies of HBV and HBcAg, DNAP, HBV-DNA at pre-treatment, pro-treatment, and follow-up stages.

Results

1.Observe long period antiviral effect from HBV replicated markers. See table 1 for details.

(1) Results of treated group, total of 20 cases are as follows:

(i) HBsAg: All cases were positive before treatment. None became negative immediately after treatment but 2 were negative when followed-up. The negative percentage over the long period is 10%(2/20).

(ii) HBcAg: 18 cases were positive before treatment and 9 cases were negative after treatment, but 3 of these returned to positive when followed-up and 1 could not be counterchecked. Another 5 cases were positive immediately after treatment but returned to negative when we performed a follow-up observation. The negative percentage over the long period is 58.8% (10/17), and the antibody-Hbe markers for 6 cases returned to positive.

(iii) HBcAg: 20 cases had all been checked before treatment and 5 of them were positive. After treatment, 1 patient returned to negative as well as in the follow-up stage. Another 2 cases were positive after treatment, but returned to negative during follow-up observations. The negative percentage is 60% (3/5).

(iv) DNAP: 17 cases had been checked before treatment and 7 of them were positive. After treatment, 5 cases returned to negative, but 1 of these was positive again in the follow-up

stage. One case that was positive in pre-treatment was not counterchecked, nor was another case that was negative in pre-treatment. The negative percentage in the long period is 60% (3/5).

(v) HBV-DNA: 18 cases had been checked before treatment and 17 of them were positive. After treatment, 7 cases returned to negative, while another 4 that were positive after treatment became negative during follow-up observations. One case that was positive in pre-treatment was not counterchecked, nor was another case that was negative in the pre-treatment stage. The negative percentage in the long period is 60.6% (10/15).

(2) Results of contrast group, total 13 cases:

(i) HBsAg: 12 cases showed positive before treatment and none of them returned to negative after treatment and in followed-up stage.

(ii) HBeAg: 12 cases were positive before treatment, 6 of them returned to negative after treatment, while 2 of these were positive again in follow-up observations, another 2 cases were not negative until the follow-up stage. The negative percentage in the long period is 50% (6/12), and in 5 cases, antibody-Hbe markers returned to a positive percentage.

(iii) HBcAg: 13 cases had been checked before treatment and 3 of them were positive. None were negative after treatment, but 1 returned negative in the follow-up stage. One case was not

counterchecked. The negative percentage in the long period is 50% (1/2).

(iv) DNAP: 12 cases had been checked before treatment, 3 of which were positive. 2 cases returned to negative immediately after treatment, and another 1 was negative in the follow-up stage. The negative percentage is 100% (3/3).

(v) HBV-DNA: 13 cases had been checked before treatment, 9 of which were positive. 2 cases returned to negative after treatment, 1 of which returned to positive again on follow-up. Another 2 cases that were positive after treatment returned to negative in the follow-up stage. 3 cases were not counterchecked. The negative percentage in the long period is 50%(3/6).

Table 1. Follow-up Observation of

The Antiviral Effect in the two groups

	HBeAg			HBcAg			DNAP			HBV-DNA		
Group	Num. of (+)	Num. of (-)	Negative Percentage	Num. of (+)	Num. of (-)	Negative Percentage	Num. of (+)	Num. of (-)	Negative Percentage	Num. of (+)	Num. of (-)	Negative Percentage
Treated Group	17	10	58.8	5	3	50	5	3	60	15	10	66.6
Contrast Group	12	6	50	2	1	50	3	3	100	6	3	50
P-Value	>0.05			>0.05			>0.05			>0.05		

/3

2. Observed comprehensive antiviral effect in the long period from 4

HBV replicated markers (HBeAg, HBcAg, DNAP, and HBV-DNA). The number of patients who had been checked for all 4 markers were 18 in the treated group and 10 in the contrast group. Results are listed in table 2.

Table 2. The change in HBV

Four replicated markers in the two groups

Group	4-	1+	2+	3+	4+
Treated Group	4	7	3	2	1
Contrast Group	0	2	6	2	0

According to the above table, we find that 4 patients from a total of 18 in the treated group were negative for all 4 markers (2 of them were negative for HAsAg, as well). 7 cases had only one positive marker, thus the total effect rate was 61.1% (11/18). None of the 10 cases in the contrast group wasd negative for all 4 markers, and only 2 patients returned to negative in one marker. The total effect rate is 20% (2/10). Comparing the two groups for $P<0.01$, the antiviral effect of the combined treatment of small dosage for interferon and thymosin was prominent for the single treatment.

3.Liver function inspection (Only based on GPT results): 14 among 19 cases (73.7%) in the treated group were normal in the follow-up GPT

countercheck, while 7 among 13 in the contrast group were normal (53.7%).

Discussion

According to results of this paper, the negative percentage of replicated markers (HBeAg DNAP, HBV-DNA, and HBcAg) were all over 55%. Although that shows no obvious difference from the contrast group statistically, in the treated group, 10 of 15 cases that were HBV-DNA positive before treatment returned to HBV-DNA negative, and the negative percentage of HBV-DNA in the long period reached a high rate of 66.6%. It takes more time for HBV-DNA to become negative than for HBeAg and DNAP, but that is a more valuable virus replication marker. The reason is that its negative status is more enduring and stable. And from the point of the changes of 4 HBV replicated markers, 4 cases in treated group were all returned to negative and 7 cases with only 1 marker positive, and the total effect rate reached to 61.6% versus 20% for contrast group, $p<0.01$. The result proves that the antiviral effect of the combined treatment group in the long period is prominent in the single interferon treatment group.

Major antiviral medicines for hepatitis B are interferon, acyclovir and Ara-A. But up to now, the really hopeful medicine is α-interferon. In order to increase the treatment effect of α-interferon, three kinds of methods are used[2]. 1) The method with an extended treatment period (6-12 months) and multi treatment period. It is not effective for a few patients, but Poress[3] obtained better results in

treatment for chronic Hepatitis B using α-interferon in 6-month-treatment, with 1-year follow-up observation. 9 cases among 12 DNAP and HBcAg returned to negative, 8 cases HBV-DNA returned to negative, and 6 cases HBeAg returned to negative. All patients with HBsAg was positive. The treatment result in the article is similar to the paper but it did not mention any case for all HBV markers returned to negative; 2) combined treatment of α-interferon and other antiviral medicines such as combined treatment of acyclovir and interferon, which was regarded as the most hopeful method. We also did some research in this direction and the details were exposed in other reports. Another example is combined treatment of Ara-Amp and interferon. Some people thought its toxicity was more, which brought patients intolerable pain. Although Smith[4] believed that combined treatment of interferon and Ara-A is the better method, there were only 44% of patients showed DNAP negative permanently. According to the report of Chiaramonte and others[5], among 32 cases with chronic hepatitis B treated by interferon and/or Ara-A visited 6 to 48 months after treatment (average 11 months), there was only one in 12 cases which showed I /II reaction and became stable after long-term effect. None was found that treatment effect was better than our combined treatment both in recent and aver the long period. 3) In the aspect of combined treatment of interferon and immunity preparation, many report from abroad said to use short-term hormone impulsion treatment before interferon treatment. But this method had some disadvantages and could aggravate the illness. So we use combined treatment of a small dosage of interferon and thymosin for safety.

According to the antiviral effect in recent and long period showed in previous report and this paper, the results of this method were all better than the contrast group. This may be because the combined application of these two medicines causes them to complement each other, so the antiviral effect is increased. The antiviral mechanism of interferon is to restrain virus replication while thymosin promotes immature T cells becoming immune-active mature T cells. The virus infecting our body has to be cleaned up by T lymphocytes. For 17 cases with HBeAg positive under interferon treatment, Ogawe[6] observed immune parameters such as OKT4+, OKT8+, 2′-5′ oligoadenylate synthetase, β2-MG (Microglobulin) of human peripheral blood mononuclear cells and liver cells, and found that the effect of interferon to increase immunity was not very strong and possibly the immunity adjustment preparations should be used to accompany interferon to be more effective. We have already tested E-RFOC forming rate and lipase before and after treatment for 14 cases under a combined treatment of interferon and thymosin and noticed the E-RFOC forming rate and lipase activity both increased after treatment, between which the increasing of E-RFOC forming rate is more obvious with statistic meaning. It indicated that thymosin played a role to increase immunity function of T cells and be helpful to the antiviral function of interferon. As some reports[7] said that thymosin could induce the creation of interferon, plus the antiviral effect of the combined treatment in recent and over the long period, we believe that the antiviral treatment by the combination of

interferon and thmysin for chronic hepatitis B is reasonable and worth further studies.

CITED LITERATURE

Reference

1) Huang hua-fang et al, 1987, 实验和临床病毒学杂志（1）：30
2) Hoofnegle et al 1987,病毒性肝炎与肝病国际讨论会文摘汇编，page 164, Shanghai medicine scientific information institution.
3) Poress ct al, 1985, *Hepatology Suppl*, 2:321
4) Smith et al, 1988, *JAMA 24(16)*: 261
5) Chisramonto el al, 1982, *Hepato-gastroenterol* 29:13
6) Ogawe et al 1987,病毒性肝炎与肝病国际讨论会文摘汇编，page 168, Shanghai medicine scientific information institution.
7) Zeng Jun-guo, 1983, 实用内科杂志,5: 237